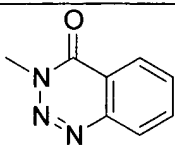
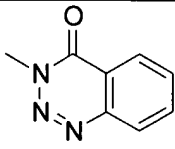


CN		rac	or
OCF ₃		rac	.

6. (Amended) A pharmaceutical composition which as active constituent contains at least one compound according to claim 5 mixed together with at least one pharmaceutically tolerable essentially non-toxic vehicle or excipient.
7. (Amended) A process for the preparation of a pharmaceutical composition according to claim 6 , comprising formulating a compound of claim 5 with at least one pharmaceutically tolerable essentially non-toxic vehicle or excipient.

Remarks / Explanations

As a result of this preliminary amendment, claims 1-8 are pending in the application. No new matter has been added.

Claims 1-7 have been amended to bring them into a form more in keeping with standard US practice.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **“Version with markings to show changes made.”**

In view of the above amendments and explanations, this application is deemed to be in condition for allowance, and allowance is accordingly requested.

Respectfully submitted,

Reg. No. 31018

Phone: (203) 812-2712

Date: _____

William F. Gray

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400 Morgan Lane

West Haven, CT 06516-4175

Version with markings to show changes made:**In the claims:**

Claims 1-7 have been amended as shown below:

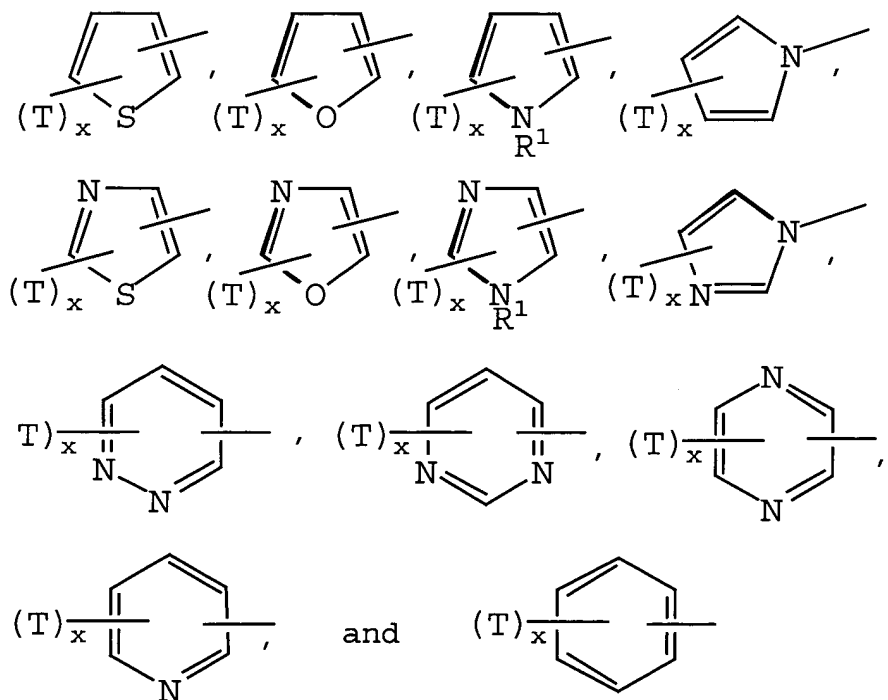
Unamended claim 8 is shown in the list below for the convenience of the examiner.

1. (Amended)[Use of the compounds] A method for the treatment or prophylaxis of multiple sclerosis, comprising administering to a mammal an effective amount of a compound of the generalized formula (I):



wherein

- (a) $(T)_x A$ represents a substituted or unsubstituted aromatic or heteroaromatic moiety selected from the group consisting of:



wherein R^1 represents H or alkyl of 1 - 3 carbons; and

each T represents a substituent group, independently selected from the group consisting of:

- * the halogens -F, -Cl, -Br, and -I;
- * alkyl of 1 - 10 carbons;
- * haloalkyl of 1 - 10 carbons;
- * haloalkoxy of 1-10 carbons;
- * alkenyl of 2 - 10 carbons;
- * alkynyl of 2 - 10 carbons;
- * $-(CH_2)_pQ$, wherein
 p is 0 or an integer 1 - 4,
- * -alkenyl-Q, wherein
said alkenyl moiety comprises 2 - 4 carbons; and
- * -alkynyl-Q, wherein
said alkynyl moiety comprises 2-7 carbons; and

Q is selected from the group consisting of aryl of 6 - 10 carbons, heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, -CN, -CHO, -NO₂, -CO₂R², -OCOR², -SOR³, -SO₂R³, -CON(R⁴)₂, -SO₂N(R⁴)₂, -C(O)R², -N(R⁴)₂, -N(R²)COR², -N(R²)CO₂R³, -N(R²)CON(R⁴)₂, -CHN₄, -OR⁴, and -SR⁴;

wherein

R^2 represents H;

alkyl of 1 - 6 carbons;
aryl of 6 - 10 carbons;
heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom; or
arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons; or

heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

R³ represents alkyl of 1 - 4 carbons;

aryl of 6 - 10 carbons;

heteroaryl comprising 4 - 9 carbons and at least one N, O or S heteroatom; or

arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons; or

heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

R⁴ represents H;

alkyl of 1 - 12 carbons;

aryl of 6 - 10 carbons;

heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;

arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons;

heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

alkenyl of 2 - 12 carbons;

alkynyl of 2 - 12 carbons;

-(C_qH_{2q}O)_rR⁵ wherein q is 1-3; r is 1 - 3; and R⁵ is H provided q is greater than 1, or alkyl of 1 - 4 carbons, or phenyl;

alkylenethio terminated with H, alkyl of 1-4 carbons, or phenyl;

alkyleneamino terminated with H, alkyl of 1-4 carbons, or phenyl]

-(CH₂)_sX wherein s is 1 - 3 and X is halogen;

-C(O)OR²; or

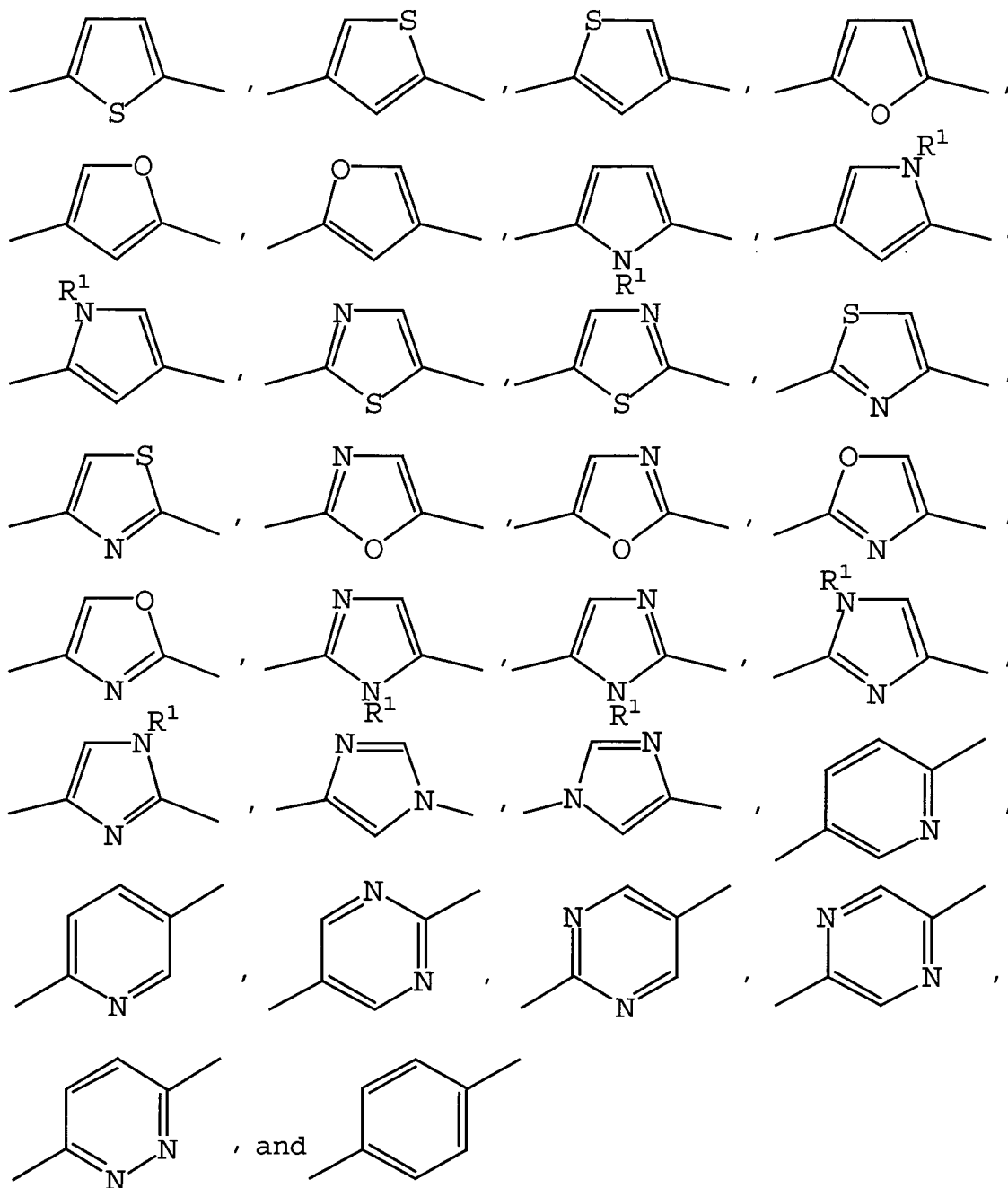
-C(O)R²;

and with the provisos that a) when two R⁴ groups are situated on a nitrogen, they may be joined by a bond to form a heterocycle, and b)

unsaturation in a moiety which is attached to Q or which is part of Q is separated from any N, O, or S of Q by at least one carbon atom, and

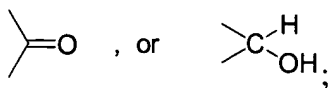
x is 0, 1, or 2;

- (b) B represents a bond or an optionally substituted aromatic or heteroaromatic ring containing 0-2 substituents T, which substituents T may independently have the meaning specified under (a), the B rings being selected from the group consisting of:



wherein R^1 is as defined above; and each R^1 may be the same or different:

(c) D represents



- (d) E represents a chain of n carbon atoms bearing m substituents R^6 , wherein said R^6 groups are independent substituents, or constitute spiro or nonspiro rings in which
- a) two groups R^6 are joined, and taken together with the chain atom(s) to which said two R^6 group(s) are attached, and any intervening chain atoms, constitute a 3 - 7 membered ring, or
 - b) one group R^6 is joined to the chain on which said one group R^6 resides, and taken together with the chain atom(s) to which said R^6 group is attached, and any intervening chain atoms, constitutes a 3 - 7 membered ring; and wherein

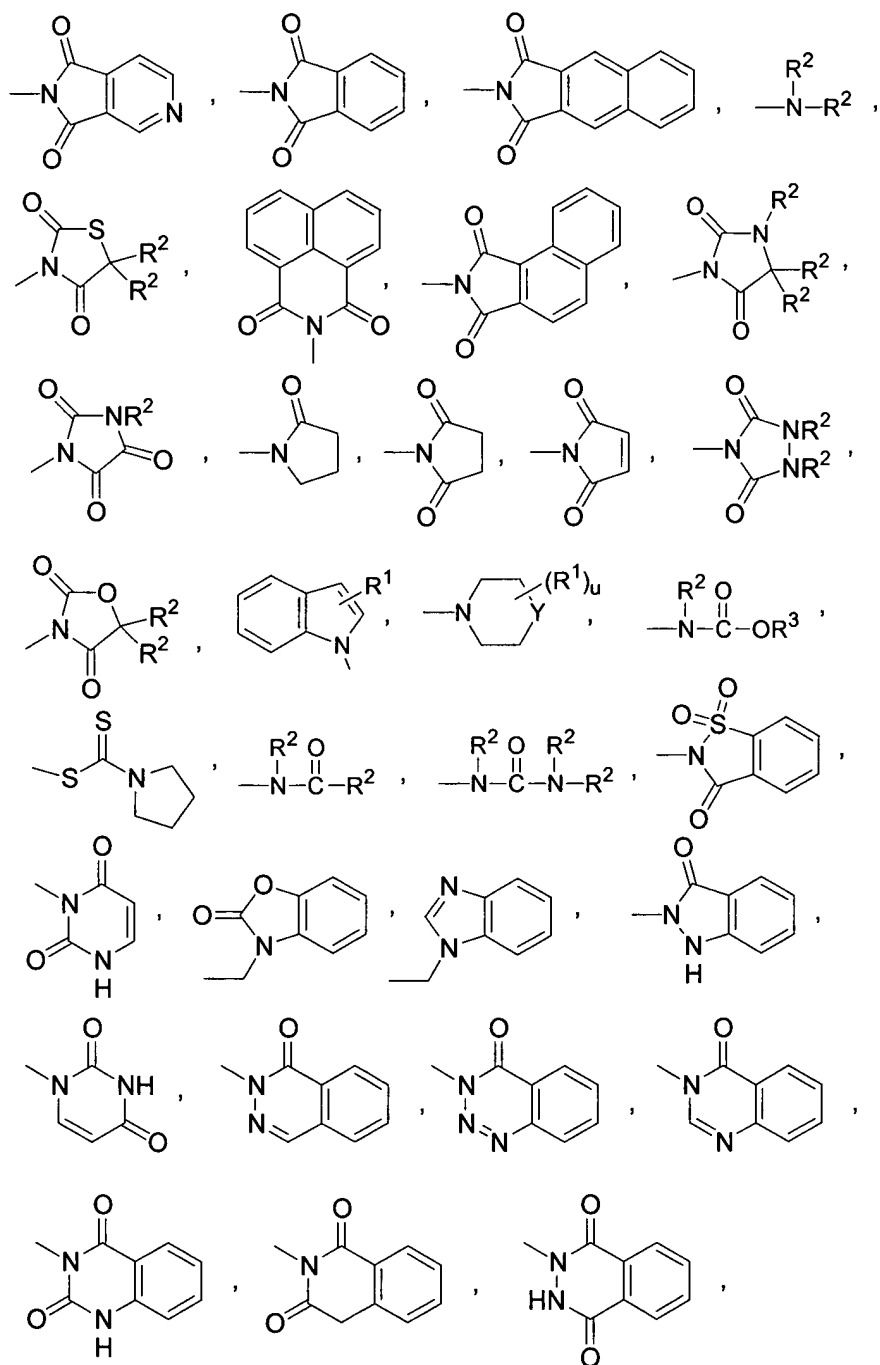
n is 2 or 3;

m is an integer of 1 - 3;

each group R^6 is independently selected from the group consisting of:

- * fluorine;
- * hydroxyl, with the proviso that a single carbon may bear no more than one hydroxyl substituent;
- * alkyl of 1 - 10 carbons;
- * aryl of 6 - 10 carbons;
- * heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;
- * arylalkyl wherein the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 8 carbons;
- * heteroaryl-alkyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 8 carbons;
- * alkenyl of 2 - 10 carbons;
- * aryl-alkenyl wherein the aryl portion contains 6 - 10 carbons and the alkenyl portion contains 2 - 5 carbons;
- * heteroaryl-alkenyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkenyl portion contains 2 - 5 carbons;
- * alkynyl of 2 - 10 carbons;

- * aryl-alkynyl wherein the aryl portion contains 6 - 10 carbons and the alkynyl portion contains 2 - 5 carbons;
- * heteroaryl-alkynyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkynyl portion contains 2 - 5 carbons;
- * $-(CH_2)_tR^7$ wherein
t is 0 or an integer of 1 - 5; and
 R^7 is selected from the group consisting of



and corresponding heteroaryl moieties in which the aryl portion of an aryl-containing R^7 group comprises 4 - 9 carbons and at least one N, O, or S heteroatom;

wherein

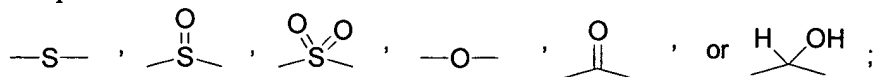
Y represents O or S;

R^1 , R^2 , and R^3 are as defined above; and each R^1 , R^2 or R^3 may be the same or different; and
 u is 0, 1, or 2; and

* $-(CH_2)_vZR^8$ wherein

v is 0 or an integer of 1 to 4; and

Z represents



R^8 is selected from the group consisting of:

alkyl of 1 to 12 carbons;

aryl of 6 to 10 carbons;

heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;

arylalkyl wherein the aryl portion contains 6 to 10 carbons and the alkyl portion contains 1 to 4 carbons;

heteroaryl-alkyl wherein the aryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

$-C(O)R^9$ wherein R^9 represents alkyl of 2 - 6 carbons, aryl of 6 - 10 carbons, heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, or arylalkyl in which the aryl portion contains 6 - 10 carbons or is heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 4 carbons;

and with the provisos that

- when R^8 is $-C(O)R^9$, Z is S or O;

- when Z is O, R^8 may also be $-(C_qH_{2q}O)_rR^5$ wherein q , r , and R^5 are as defined above; and

* $-(CH_2)_wSiR^{10}_3$ wherein

w is an integer of 1 to 3; and

R^{10} represents alkyl of 1 to 2 carbons;

and with the proviso that

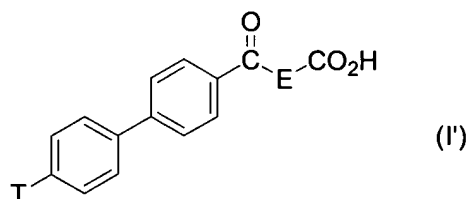
- aryl or heteroaryl portions of any of said T or R⁶ groups optionally may bear up to two substituents selected from the group consisting of -(CH₂)_yC(R⁴)(R³)OH, -(CH₂)_yOR⁴, -(CH₂)_ySR⁴, -(CH₂)_yS(O)R⁴, -(CH₂)_yS(O)₂R⁴, -(CH₂)_ySO₂N(R⁴)₂, -(CH₂)_yN(R⁴)₂, -(CH₂)_yN(R⁴)COR³, -OC(R⁴)₂O- in which both oxygen atoms are connected to the aryl ring, -(CH₂)_yCOR⁴, -(CH₂)_yCON(R⁴)₂, -(CH₂)_yCO₂R⁴, -(CH₂)_yOCOR⁴, -halogen, -CHO, -CF₃, -NO₂, -CN, and R³ wherein

y is 0 - 4; and

R³ and R⁴ are as defined above, and each R³ and R⁴ may be the same or different; and any two R⁴ which are attached to one nitrogen may be joined to form a heterocycle;

[and] or a pharmaceutically acceptable salt[s and] or prodrug[s] thereof [for the manufacturing of drugs for the treatment and prevention of multiple sclerosis].

2. (Amended)[Use] The method according to claim 1 wherein the method comprises administering [of] a compound[s] of the general formula (I')

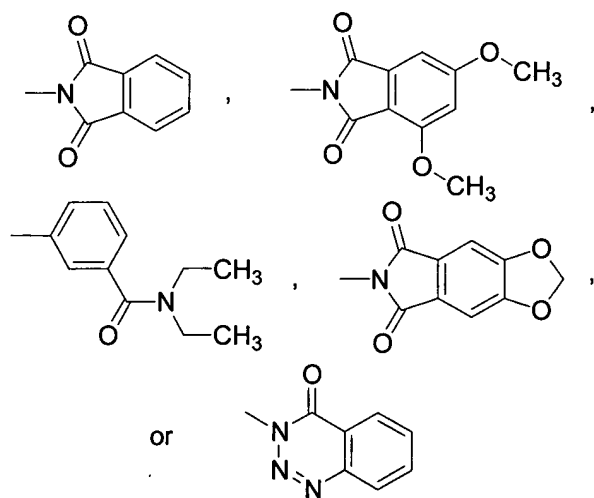


wherein

T is (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy, chloride, bromide, fluoride, acetoxy, hydroxy, cyano, trifluoromethyl or trifluoromethoxy,

CO-E-CO₂H represents a 3-carboxyl-5-(R⁷)-pentan-1-on-1-yl- or a [2-carboxyl-3-(R⁷)-methyl-cyclopentan-1-yl]-carbonyl-residue, wherein

R⁷ represents a group of the formula



[and their salts] or a salt thereof.

3. (Amended)[Use] The method according to claim 2, characterized in that [the] one enantiomer of a pair of enantiomers at a chiral center adjacent to the carboxylic acid moiety of the group of the formula CO-E-CO₂H in compounds of the general formula (1') more potently inhibits MMP-2 and/or MMP-9.

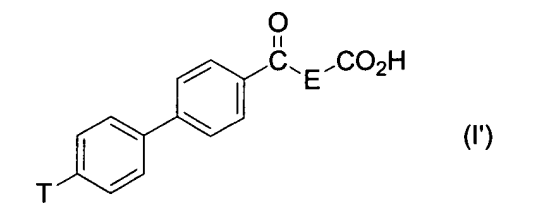
4. (Amended)[Use] The method according to claim 1, wherein the compound is selected from the group consisting of

(+)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-(4'-ethoxyl[1,1'-biphenyl]-4-yl)-4-oxobutanoic acid,

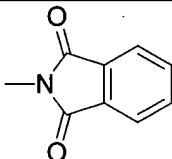
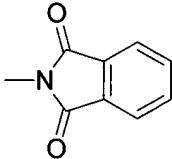
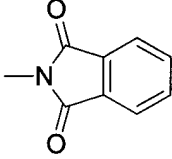
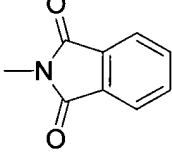
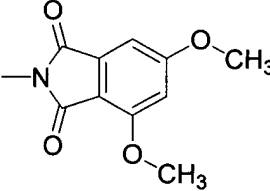
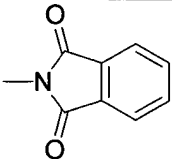
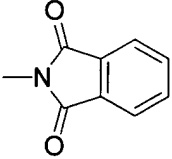
(+)-4-(4'-chloro[1,1'-biphenyl]-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-oxobutanoic acid,

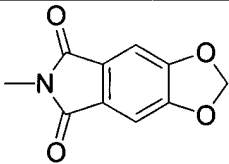
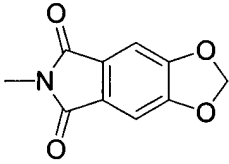
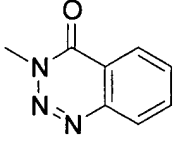
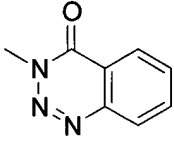
[or a salt] and salts thereof.

5. (Amended) [Compounds] A compound of the general formula (I'),



wherein CO-E-CO₂H represents a 3-carboxyl-5-R⁷-pentan-1-on-1-yl- residue, and wherein T and R⁷ have the meaning indicated in the following table:

T	R ⁷	racemate, (+)- or (-)-enantiomer	
OEt		(+)	;
OEt		(-)	;
OAc		rac	;
OH		rac	;
Cl		rac	;
Br		(+)	;
Br		(-)	;

C1		(+)	;
C1		(-)	;
CN		rac	or
OCF ₃		rac	.

6. (Amended)[Pharmaceutical] A pharmaceutical composition which as active constituent contains at least one compound according to claim 5 mixed together with at least one pharmaceutically tolerable essentially non-toxic vehicle or excipient.

7. (Amended) [Process] A process for the preparation of a pharmaceutical composition according to claim 6 , comprising formulating a compound of claim 5 with at least one pharmaceutically tolerable essentially non-toxic vehicle or excipient.

8. Compound according to claim 5 for use as a medicament in the treatment of humans or animals.